Remarks

Claims 29-41 were pending in the subject application. By this Amendment, claims 29 and 35 have been amended, claims 30, 31, 33, 34, and 36-38 have been cancelled, and new claims 42-51 have been added. The undersigned avers that no new matter is introduced by this amendment. Entry and consideration of the amendments presented herein is respectfully requested. It should be understood that the amendments presented herein have been made solely to expedite prosecution of the subject application to completion and should not be construed as an indication of the applicants' agreement or acquiescence in the Examiner's position. Accordingly, claims 29, 32, 35, and 39-51 are currently before the Examiner for consideration. Favorable consideration of the pending claims is respectfully requested.

Submitted herewith is a supplemental Information Disclosure Statement (IDS), accompanied by the form PTO/SB/08 and copies of the references listed therein. The applicants respectfully request that the references listed on the form PTO/SB/08 be considered and made of record in the subject application.

As an initial matter, the Examiner indicates that the specification is objected to because it contains an embedded hyperlink. The applicants respectfully submit that the specification was amended to delete the embedded hyperlink by the applicants' Supplemental Amendment under 37 C.F.R. §1.111 submitted to the Patent Office on May 17, 2005. A copy of the return-receipt post card is submitted herewith for the Examiner's convenience. The applicants respectfully request that this objection be withdrawn.

The application is also objected to on the grounds that the subject specification fails to comply with the requirements of 37 C.F.R. §§1.821 through 1.825. Specifically, the Examiner indicates that the sequences shown in Figures 2, 3, and 7 are missing numeric sequence identifiers. By this Amendment, the applicants have amended the subject specification to include the SEQ ID NOs. for these sequences (SEQ ID NOs:11-18). Support for these amendments can be found, for example, in Figures 2, 3, and 7, and in paragraphs [0051], [0052], [0054], and [0070] at pages 20-22 and 33-34 of the specification as originally filed. A Submission of Sequence Listing under §1.821, including a replacement sequence listing on paper and a computer readable format is attached. A

Notice to Comply with Requirements for Patent Applications Containing Nucleotide Sequence and/or Amino Acid Sequence Disclosures was attached with the outstanding Office Action and a copy of the Notice is attached herewith. Reconsideration and withdrawal of the objection is respectfully requested.

By this Amendment, claims 29 and 35 have been amended, and claims 42-51 have been added. Claims 29, 32, 35, and 39-42 are now drawn to a method for inducing proliferation of human stem cells. New claims 43-49 are drawn to a method for inducing proliferation of mouse stem cells. Support for the amendments to claims 29 and 35 can be found, for example, at page 30, lines 16-18 of paragraph [0065]; page 4, paragraphs [0010] and [0011], of the subject specification, and the claims as originally filed. Claims 43-49 correspond to claims 29, 32, 35, and 39-42, but recite mouse stem cells instead of human stem cells, and recite s-SHIP instead of SIP-110. New claim 50 is drawn to a method for inducing proliferation of human hematopoietic stem cells or human embryonic stem cells. New claim 51 is drawn to a method for inducing proliferation of mouse hematopoietic stem cell or mouse embryonic stem cells.

Claims 29-41 have been rejected under 35 U.S.C. §112, first paragraph, as non-enabled by the subject specification. The applicants respectfully traverse and submit that the claimed invention is fully enabled by the subject specification.

The methods of the claimed invention are reasonably enabled by the specification, as one of ordinary skill in the art would be able to make and use the invention without undue experimentation. By this Amendment, claim 29 has been amended to recite that an anti-SIP-110 shRNA is introduced into human stem cells. New claim 43 recites that an anti-s-SHIP shRNA is introduced into mouse stem cells. The term "inhibitor" has been removed from the claims. Claim 30, which recited that the inhibitor is a dominant-negative mutant, has been canceled.

The Office Action raises issues pertaining to: (1) the effects of reducing s-SHIP expression; and; and (2) utilization of shRNA to reduce s-SHIP expression. The applicants have addressed these issues in that order.

At page 6, the Office Action indicates that the patent application does not demonstrate that introduction of anti-SHIP shRNA results in induction of stem cell proliferation. Submitted herewith for the Examiner's consideration is a Declaration by Dr. William G. Kerr under 37 C.F.R. §1.132,

accompanied by Exhibits A-D. It has been known for some time that SHIP1 (also known as SHIP), the full-length hematopoietic isoform, opposes PI3K and, thus, PI3K-effector pathways, which control cell proliferation and/or survival. As indicated by Dr. Kerr in the Declaration, "that SIP-110/s-SHIP may also do this in a pluripotent stem cell, and perhaps other stem cell populations, is a reasonable expectation". Dr. Kerr's laboratory has found that a loss-of-function mutation of SHIP results in expansion of the hematopoietic stem cell (HSC) compartment *in vivo*. Submitted with Dr. Kerr's Declaration as Exhibit B is the unpublished manuscript entitled "SHIP-deficiency enhances HSC Proliferation and Survival but Comprises Repopulating Potential", which is currently under review by the journal *Blood*. As described in Exhibit B, Dr. Kerr's laboratory has demonstrated that $SHIP^{-/-}$ mice generated by a Cre-lox mutation strategy have an expanded HSC compartment and, based on direct cell cycle analysis of HSC with Hoechst dye, they have shown that this is due to enhanced HSC proliferation (see, for example, the pages 5-7 and 12-15 of Exhibit B). Likewise, Helgason *et al.* made the same inference based on the observation that 5-FU treatment damaged the marrow-repopulating ability of $SHIP^{-/-}$ mice and, therefore, presumably killed proliferating HSC (see Helgason *et al.*, *Blood*, 2003, 102:3541-3547, which is cited in the outstanding Office Action).

At page 6, the Office Action cites Helgason *et al.* as showing that when Pep3b mice received transplants of various repopulation doses of bone marrow cells from $SHIP^{+/+}$ or $SHIP^{-/-}$ mice, the frequency of donor-derived cells in the recipients of $SHIP^{-/-}$ bone marrow cells was significantly lower than in $SHIP^{+/+}$ cells at 16 weeks post-transplantation. Thus, the Office Action indicates that Helgason *et al.* teach that mice having a disrupted SHIP1 gene have defects in hematopoietic proliferation, instead of increased proliferation. The data in Exhibit B indicates that although SHIP deficiency does damage HSC repopulating potential, this is likely due to effects on the ability of SHIP-deficient HSC to <u>home</u> to bone marrow, where they reside after transplantation (see, for example, pages 11 and 13-15 of Exhibit B). Thus, as stated by Dr. Kerr, "the findings of Helgason *et al.* are not germane to the enhancement of stem cell proliferation by reducing SIP-110/s-SHIP gene expression."

At page 6, the Office Action indicates that the patent application does not demonstrate that the stem cells can differentiate into any cell type. As an initial matter, the applicants note that claims 41 and 48 only require that the cells are induced <u>to differentiate</u>. No particular cell phenotype or

extent of differentiation is recited in the claims. Cell differentiation is a process in which the cell progresses from an undifferentiated state to a differentiated state, developing characteristics of a mature cell (such as cell morphology or the expression of characteristic cell markers). Furthermore, as methods for inducing differentiation of primitive cells were known in the art at the time the application was filed, it is not necessary that they be included in the subject specification. As stated by Dr. Kerr, "the scientific literature is replete with publications describing the differentiation of stem cells into various mature cells types *in vitro* and *in vivo*." The ultimate differentiated cell type depends upon the differentiation potential of the particular type of stem cell and the conditions to which the stem cell is exposed. Various culture media, culture techniques, and differentiation agents useful for inducing differentiation of stem cells are well known in the art and thus, need not be included in the subject application. The applicants submitted copies of several scientific publications with the Amendment dated April 29, 2005 (Shah *et al.*, *Cell*, 1996, 85:331; White *et al.*, *Neuron*, 2001, 29:57; Watt *et al.*, *Science*, 2000, 287:1427; Lee *et al.*, *Nat. Biotechnol.*, 2000, 18:675; Lumelsky *et al.*, *Science*, 2001, 292:1389), which describe the use of a variety of agents to induce differentiation of various stem cell types. Furthermore, appendix D of Exhibit C, which accompanies Dr. Kerr's Declaration, contains tables with scientific publications reporting the differentiation of mouse and human stem cells, along with the differentiation conditions utilized. As stated by Dr. Kerr, "I am not aware of any scientific evidence to suggest that the differentiation conditions reported in the scientific literature cannot be utilized to differentiate stem cells that have been induced to proliferate by reducing SIP-110/s-SHIP gene expression." As the Examiner is aware, the specification need not disclose what is well-known to those skilled in the art and preferably omits that which is well-known to those skilled and already available to the public. *In re Buchner*, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991); *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 231 USPQ 81, 94 (Fed. Cir. 1986), *cert. denied*, 480 U.S. 947 (1987); and *Lindemann Maschinenfabrik GMBH v. American Hoist & Derrick Co.*, 221 USPQ 481, 489 (Fed. Cir. 1984).

At page 8, the Office Action indicates that the patent application does not teach that administration of anti-SHIP shRNA results in proliferation of other stem cells, such as neuronal stem cells and osteoblastic stem cells. As indicated above, Dr. Kerr's laboratory has found that proliferation of HSC is increased by SHIP deficiency in these cells. As stated by Dr. Kerr, "it is

reasonable to conclude that this may also be the case in other stem cells that express SHIP or SIP-110/s-SHIP and utilize it to oppose PI3K." By this Amendment, the applicants have amended claim 29 to recite that the human stem cells express SIP-110. Likewise, new claim 43 recites that the mouse stem cells express s-SHIP. New independent claim 50 recites that the human stem cells are hematopoietic stem cells or embryonic stem cells. New independent claim 51 recites that the mouse stem cells are hematopoietic stem cells or embryonic stem cells.

The Office Action indicates that the subject application does not adequately teach how to make shRNA that reduce expression of s-SHIP in stem cells and, consequently, induce proliferation. Having the structure and sequence of the target gene (SIP-110 or s-SHIP), the applicants submit that one skilled in the art could readily obtain target sequences within the stem cells' s-SHIP or SIP-110 mRNA. Furthermore, due to the certainty of the genetic code and complementarity, and the mechanism of RNAi, there is a well known correlation between target nucleic acid sequences within a target gene and nucleic acid sequences that interfere with the expression of the target gene. Hence, having the nucleotide sequence of the target gene provides sufficient information to allow one skilled in the art to obtain candidate interfering RNA molecules without resort to undue experimentation.

While it is true that not all RNA molecules will inhibit a target gene, the availability of target gene sequence information, the capability to synthesize potentially interfering RNA molecules in large quantities, and the knowledge of those skilled in the art increase the likelihood of obtaining gene silencing RNA molecules. Thus, the probability of finding an individual functional interfering RNA molecule among rationally designed candidates is **very high**, and screening for such RNA molecules does not involve undue experimentation.

Submitted herewith as Exhibit D is the shRNA sequence used to knockdown s-SHIP in embryonic stem cells, as described in paragraph [0071] at page 34 of the subject specification, and the mRNA sequence of mouse s-SHIP (Accession No. AF184912) from GenBank's sequence viewer. The s-SHIP target is indicated (nucleotides 683-704 of Accession AF184912). As indicated by Dr. Kerr, "the results achieved with the s-SHIP-specific interfering RNA in the experiment described in the patent application are reasonably predictive of other interfering RNA molecules specific for s-SHIP or SIP-110."

At page 9, the Office Action indicates that accessibility of target mRNA is an obstacle to making functional shRNA molecules. The applicants submit that it is art-recognized that RNAi differs from antisense-mediated interference in both approach and effectiveness. Compared to antisense or ribozyme technology, the secondary structure of the target mRNA does not appear to have a strong effect on RNAi-mediated silencing (see Harborth J. *et al.*, *J. Cell Sci.*, 2001, Dec., 114 (Pt. 24):4557-4565, which accompanies the IDS submitted herewith). In fact, RNAi has now become such a popular tool for gene silencing, many companies use proprietary algorithms to design and chemically synthesize interfering RNA molecules using a conventional DNA/RNA synthesizer. Research groups have created human shRNA libraries that target thousands of genes and have used them to identify new genes (see pages 80-81 and 84 of Bonetta, L. "RNAi: Silencing never sounded better" *Nature Methods*, 2004, 1(1):79-86), which accompanies the IDS submitted herewith).

As the Examiner is aware, a specification is initially presumed to be in compliance with the enablement requirement of §112, first paragraph. The burden is on the Patent Office to establish a reasonable basis to question enablement. *In re Wright*, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993). The test of enablement is whether one of ordinary skill in the art could make and use the claimed invention from the teachings of the patent application, coupled with information known in the art, without undue experimentation. For an Office Action to sustain a rejection on the grounds of enablement, it must provide evidence that the claimed method could not be performed without undue experimentation.

The proper standard for compliance with the enablement requirement is not absolute predictability but objective enablement. Evidence provided by the applicants nees not be conclusive but merely convincing to one of skill in the art (see MPEP 2164.05). In other words, a patent specification need not set forth clear and convincing evidence "proving" its conclusions. Rather, the applicants' statements and assertions are to be taken as true, and rejected only if the underlying facts are found to be untruthful or inaccurate, *i.e.*, only if the asserted claim is "incredible" or "impossible." *In re Marzocchi*, 169 USPQ 367, 370 (CCPA 1971).

The experimental evidence in the subject specification is sufficiently compelling and fully supports the assertion that s-SHIP and SIP-110 play a dominant role in cell growth. In view of the

evidence submitted to the Patent Office, it is certainly not "unreasonable" for the applicants to suggest that stem cell proliferation can be induced by inhibiting s-SHIP or SIP-110 expression.

In regard to the working example described in paragraph [0071] at page 34 of the patent application, the results of which are shown in Figure 8, the applicants submit that all that is required by the patent laws is that a "reasonable correlation" exist between the scope of the claims and the scope of enablement. *In re Brana*, 34 USPQ2d 1436, 1441 (Fed. Cir. 1995) and MPEP 2164.02. A rigorous or an invariable exact correlation is not required, as stated in *Cross v. Iizuka*, 224 USPQ 739, 747 (Fed. Cir. 1985):

> [B]ased upon the relevant evidence as a whole, there is a reasonable correlation between the disclosed *in vitro* utility and an *in vivo* activity, and therefore a rigorous correlation is not necessary where the disclosure of pharmacological activity is reasonable based upon the probative evidence. (Citations omitted.)

If a particular model is recognized as correlating to a specific condition, then it should be accepted as such unless there is evidence that the model does not correlate. Since the initial burden is on the Examiner to give reasons for lack of enablement, reasons must also be given for a conclusion of lack of correlation for an *in vitro* model. Thus, the applicants respectfully submit that the *in vitro* model within the specification is sufficiently predictive of activity in mouse and human stem cells *in vitro* and *in vivo*. As such, the pending claims are commensurate in scope with the experimental findings of the instant disclosure and enabled thereby.

Given the state of the art as demonstrated by the scientific publications submitted herewith, and the information provided in the subject specification and the experimental results obtained therewith, one of ordinary skill in the art can target and reduce expression of s-SHIP and SIP-110, without resort to undue experimentation. Thus, the applicants respectfully submit that the subject specification enables the methods as currently claimed.

The applicants respectfully submit that the subject specification contains sufficient information to enable one of ordinary skill in the pertinent art to make and use the claimed invention without undue experimentation. Accordingly, the applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. §112, first paragraph.

Claims 29-41 have been rejected under 35 U.S.C. §112, first paragraph, as lacking sufficient written description. The applicants traverse and respectfully submit that the subject specification provides a sufficient written description of the claimed invention.

As indicated above, by this Amendment, claim 29 has been amended to recite that an anti-SIP-110 shRNA is introduced into human stem cells. New claim 43 recites that an anti-s-SHIP shRNA is introduced into mouse stem cells. The term "inhibitor" has been removed from the claims. Claim 30, which recited that the inhibitor is a dominant-negative mutant, has been canceled.

The Office Action indicates that the subject application does not adequately describe shRNA specific for s-SHIP. Further, the Office Action indicates that the subject application does not provide the nucleic acid sequence for the anti-s-SHIP shRNA referred to in paragraph [0071] at page 34 of the subject specification, or other nucleic acid sequences that function as anti-s-SHIP shRNA.

The subject specification contains sufficient disclosure to convey to one of ordinary skill in the art that the applicants had possession of the concept of what is claimed, which is all that is necessary to satisfy the written description requirement under 35 U.S.C. §112, first paragraph. The teaching of the subject application and knowledge of the sequence and structure of the s-SHIP and SIP-110 genes provides sufficient structural and functional correlates to describe the genera of interfering RNA recited in the claims.

RNA mediated interference or RNA interference (RNAi) is a term initially coined by Fire and co-workers to describe the phenomenon that double-stranded RNA (dsRNA) can block gene expression when it is introduced into nematodes (Montgomery, M.K. *et al. Proc. Natl. Acad. Sci. USA*, 1998, 95:15502-15507, which accompanies the supplemental IDS submitted herewith). RNAi has become a potent tool for suppressing gene expression in mammalian cells at the mRNA level utilizing a process of sequence-specific, post-transcriptional gene silencing. Accompanying the supplemental IDS submitted herewith are International Publication WO 99/32619 (Fire *et al.*), Tuschl T. *et al.* (*Genes & Development*, 1999, 13:3191-3197); Zamore P. *et al.* (*Cell*, 2000, 101:25-33); Svoboda P. *et al.* (*Development*, 2000, 127:4147-4156); Tuschl, T. *et al.* (*Chembiochem*, 2001, 2(4):239-245); Elbashir S. *et al.* I (*Nature*, 2001, 411:494-498); Elbashir S. *et al.* II (*Genes & Development*, 2001, 15:188-200) and Caplen N.J. *et al.* (*PNAS*, 2001, 98(17):9742-9747). RNAi is triggered by dsRNA and results in sequence-specific degradation of homologous single-stranded

target RNAs. When dsRNA containing a sequence complementary to a specific mRNA target is administered to cells, it is processed into short nucleotide fragments that guide the cleavage of the transcript. Thus, the endogenous mediators of RNAi are short (*e.g.*, 21-23-nucleotide) interfering RNAs (siRNAs) generated from the longer double-stranded RNAs by the ribonuclease III activity of the highly conserved dicer enzyme (Tuschl T. *et al.* (1999); Zamore P. *et al.*; Elbashir S. *et al.* I; and Elbashir S. *et al.* II). It has been demonstrated that RNAi-mediated gene suppression can be obtained in mammalian cells by delivery of chemically synthesized short (*e.g.*, less than 30 nucleotides) double-stranded siRNA molecules or by endogenous expression of short hairpin RNAs (shRNAs) bearing a fold-back stem-loop structure (Elbashir *et al.* I).

The interfering RNA recited in the claims are not described by function alone. As is evidenced by the aforementioned publications, structural attributes of interfering RNA, including size and content, were known in the art at the time the application was filed (see, for example, pages 197-198 of Elbashir S. *et al.* II). Elbashir *et al.* proposed directly introducing short (*e.g.*, 21-23 nucleotides) dsRNA (siRNA) into mouse and human cells to avoid the problems associated with the expression of longer dsRNAs (Elbashir S. *et al.* I). Elbashir *et al.* state,

> The finding that synthetic 21- and 22-nt siRNA duplexes can be used for efficient mRNA degradation demonstrates that the targeting step can be uncoupled from the dsRNA-processing step. This raises the prospects of using siRNA duplexes as new tools for sequence-specific regulation of gene expression in functional genomics as well as biomedical studies. The siRNA may be effective in mammalian systems, where long dsRNAs cannot be used because they activate the dsRNA-dependent protein kinase (PKR) response (Clemens 1997). As such, the siRNA duplexes may represent a new alternative to antisense or ribozyme therapeutics. (Elbashir S. *et al.* II, page 198, column 2)

The state of the art of RNAi at the application's filing date, combined with the teachings of the subject application, provide a rational basis for the design of interfering RNA specific for s-SHIP or SIP-110 mRNA. To target a specific mRNA for degradation, a portion of the mRNA sequence must be known and a segment of the target mRNA must be selected that will be used for targeting by the cognate shRNA. The design of specific shRNA that interfere with the expression of a specific gene requires accurate knowledge of at least a 20-nucleotide segment of its encoded mRNA. These requirements are met by the subject application. Having the structure and sequence of the target

gene (s-SHIP and SIP-110), and the teachings of the specification, the applicants submit that one skilled in the art would readily envision target nucleic acid sequences with the s-SHIP or SIP-110 mRNA sequence, such as the SHIP enzymatic domain. Furthermore, due to the certainty of the genetic code and complementarity, there is a well known correlation between target nucleic acid sequences within a target gene and nucleic acid sequences that interfere with the expression of the target gene. Hence, having the nucleotide sequence of the target gene provides sufficient information to one skilled in the art to obtain the interfering RNA molecules recited in the claims. Therefore, the applicants respectfully submit that the subject specification provides sufficient information regarding the genus of s-SHIP and SIP-110 mRNA and interfering RNA specific thereto.

While not all RNA molecules will inhibit a target gene, the availability of the entire s-SHIP and SIP-110 gene sequences, the capability to synthesize potentially interfering RNA molecules in large quantities, and the knowledge available to those skilled in the art at the time the application was filed (*e.g.*, International Publication WO 99/32619 (Fire *et al.*); Tuschl T. *et al.* (1999); Zamore P. *et al.* (2000); Svoboda P. *et al.*, (2000); Tuschl, T. *et al.* (2001); Elbashir S. *et al.* I (2001); and Elbashir S. *et al.* II (2001)) increase the likelihood of obtaining functioning interfering RNA molecules specific for s-SHIP or SIP-110. Thus, while the probability that any single interfering RNA molecule will be effective in gene silencing is not necessarily high, the probability of identifying an individual functional interfering RNA molecule among rationally designed candidates is **very high**.

The descriptive text needed to meet the written description requirement varies with the nature and scope of the invention at issue, and with the scientific and technological knowledge already in existence. There is no *per se* rule that in order to satisfy the written description requirement, known DNA sequences must be disclosed in the specification. Rather, the written description requirement must be considered in the context of the claimed invention and the state of knowledge in the relevant art. *Capon et al. v. Eshhar et al.*, 418 F.3d, 1349 (Fed. Cir. 2005). In Capon *et al.*, which is a case stemming from a patent interference between two parties each claiming chimeric cell surface receptors, the U.S. Court of Appeals for the Federal Circuit struck down as "an inappropriate generalization" the Board of Patent Appeals and Interference's rule that, even where the nucleotide sequences of the component DNA are known, the nucleotide sequences of the chimeric genes must

be fully presented. The Court noted "the determination of what is needed to support generic claims to biological subject matter depends on a variety of factors, such as the existing knowledge in the particular field, the extent and content of the prior art, the maturity of the science or technology, the predictability of the aspect at issue, and other considerations appropriate to the subject matter." As explained by the Court:

> [I]t is not necessary that every permutation within a generally operable invention be effective in order for an inventor to obtain a generic claim, provided that the effect is sufficiently demonstrated to characterize a generic invention.

Thus, the written description requirement states that the applicants must describe the invention; it does not state that every invention must be described in the same way. The applicants acknowledge that sequences and structural formulas provide a convenient method of demonstrating possession of many molecules; however, other identifying characteristics or combinations of characteristics may demonstrate the requisite possession. In *Enzo Biochem, Inc. v. Gene-Probe, Inc.*, 63 USPQ2d 1609 (Fed Cir. 2002), the Court reaffirmed that deposit of a physical sample may replace words when description is beyond present scientific capability. In *Amgen, Inc. v. Hoechst Marion Roussel, Inc.*, 65 USPQ2d 1385 (Fed Cir. 2003), the Court explained further that the written description requirement may be satisfied "if in the knowledge of the art the disclosed function is sufficiently correlated to a particular, known structure." For example, possession of an antibody may be demonstrated based on a description and characterization of its corresponding antigen. Disclosure of an antigen fully characterized by its structure, formula, chemical name, physical properties, or deposit in a public depository provides an adequate written description of an antibody claimed by its binding affinity to that antigen. *Noelle v. Lederman*, 69 USPQ2d 1508, 1514 (Fed. Cir. 2004) and MPEP 2163 IIA3(a). The nature of the interfering RNA of the claimed invention are clearly distinguishable from the compounds at issue in *University of Rochester v. G.D. Searle & Co.*, 69 USPQ2d 1886 (Fed. Cir. 2004), where the Court affirmed that the description of the COX-2 enzyme did not serve to describe unknown small molecules capable of selectively inhibiting the enzyme. The teaching of the subject specification and the knowledge of the sequence and structure of the s-SHIP and SIP-110 genes provide one skilled in the art with sufficient structural and functional

correlates to describe the genus of interfering RNA that suppress expression of the s-SHIP and SIP-110 genes.

Having the nucleotide sequence of the target gene provides discerning information regarding the sequences of suitable interfering RNA molecules, and leads one of ordinary skill in the art to their selection. Due to nucleotide complementarity and the mechanism of RNAi, RNA molecules likely to hybridize with s-SHIP or SIP-110 mRNA and interfere with their expression could then be determined. One of ordinary skill in the art need only be provided with the sequence of the **target gene**, as opposed to the sequence of any **particular** interfering RNA. There is no sequence information essential for carrying out the invention that is not provided in the specification or not well known to those skilled in the art.

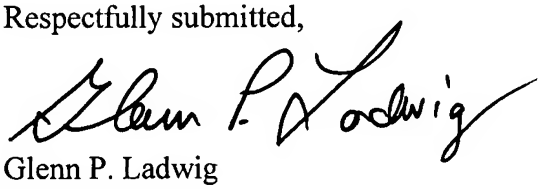
Thus, the applicants submit that the subject specification contains sufficient disclosure to convey to one of ordinary skill in the art that the applicants had possession of the concept of what is claimed, which is all that is necessary to satisfy the written description requirement of 35 U.S.C. §112, first paragraph. Accordingly, reconsideration and withdrawal of the rejection under 35 U.S.C. §112, first paragraph, is respectfully requested.

In view of the foregoing remarks and amendments to the claims, the applicants believe that the currently pending claims are in condition for allowance, and such action is respectfully requested.

The Commissioner is hereby authorized to charge any fees under 37 C.F.R. §§ 1.16 or 1.17 as required by this paper to Deposit Account 19-0065.

The applicants invite the Examiner to call the undersigned if clarification is needed on any of this response, or if the Examiner believes a telephonic interview would expedite the prosecution of the subject application to completion.

Respectfully submitted,



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Attachments: Petition and Fee for Extension of Time
Post Card Receipt for the Supplemental Amendment under 37 C.F.R. §1.111 submitted to the Patent Office on May 17, 2005
Submission of Sequence Listing under 37 C.F.R. §§1.821-1.825
Sequence Listing on paper and computer readable format
Copy of Notice to Comply
Declaration by Dr. William G. Kerr under 37 C.F.R. §1.132, with Exhibits A-D
Supplemental Information Disclosure Statement with form PTO/SB/08 and references

May 17, 2005

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APPLICANTS: Kerr, Ninos

SUBMISSION TO PTO:
1. Supplemental Amendment under 37 CFR §1.111

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